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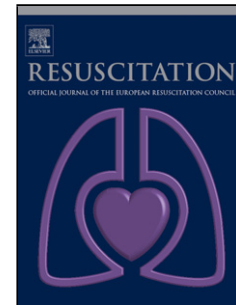
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A Randomised trial of Expedited transfer to a cardiac arrest centre for non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest: The ARREST pilot randomised trial

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Short Title: ARREST Pilot Randomised Trial

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Abstract

Background

Wide variation exists in inter-hospital survival from out-of-hospital cardiac arrest (OHCA). Regionalisation of care into cardiac arrest centres (CAC) may improve this. We report a pilot randomised trial of expedited transfer to a CAC following OHCA without ST-elevation. The objective was to assess the feasibility of performing a large-scale randomised controlled trial.

Methods

Adult witnessed ventricular fibrillation OHCA of presumed cardiac cause were randomised 1:1 to either: 1) treatment: comprising expedited transfer to a CAC for goal-directed therapy including access to immediate reperfusion, or 2) control: comprising current standard of care involving delivery to the geographically closest hospital. The feasibility of randomisation, protocol adherence and data collection of the primary (30-day all-cause mortality) and secondary (cerebral performance category (CPC)) and in-hospital major cardiovascular and cerebrovascular events (MACCE)) clinical outcome measures were assessed.

Results

Between November 2014 and April 2016, 118 cases were screened, of which 63 patients (53%) met eligibility criteria and 40 of the 63 patients (63%) were randomised. There were no protocol deviations in the treatment arm. Data collection of primary and secondary outcomes was achieved in 83%. There was no difference in baseline characteristics between the groups: 30-day mortality (Intervention 9/18, 50% vs. Control 6/15, 40%; $P=0.73$), CPC 1/2 (Intervention 9/18, 50% vs. Control 7/14, 50%; $P>0.99$) or MACCE (Intervention 9/18, 50% vs. Control 6/15, 40%; $P=0.73$).

Conclusions

These findings support the feasibility and acceptability of conducting a large-scale randomised controlled trial of expedited transfer to CAC following OHCA to address a remaining uncertainty in post-arrest care.

Keywords: Out-of-hospital Cardiac Arrest, Cardiac Resuscitation Centre, Coronary Angiography.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a global public health issue. There are 60,000 OHCA per year in the United Kingdom and over 400,000 in the United States.¹⁻³ There is wide variation in both regional and inter-hospital survival rates from OHCA and overall survival remains poor, with a reported average of 7%.⁴ The adoption of systematic approaches to post-resuscitation care may improve long-term survival from OHCA.^{5,6} Regionalisation of care into specialist centres has played a vital role in the management of time-critical illnesses through concentration of services and greater provider experience.⁷⁻¹⁴ Coronary artery disease is responsible for >70% of OHCA, with an acute occlusion demonstrated in 50% of consecutive patients taken immediately to coronary angiography.¹⁵ Multi-faceted interventions including early cardiopulmonary resuscitation (CPR) and defibrillation, followed by timely reperfusion are associated with reduced risk of re-arrest, reduced myocardial dysfunction and thus improved outcomes following cardiac arrest from ST-elevation (STE) myocardial

infarction.¹⁶⁻¹⁸The International Liaison Committee on Resuscitation (ILCOR) suggests transport of all post-arrest patients to a cardiac arrest centre (CAC) with 24/7 access to interventional cardiology facilities to manage the ensuing cardiovascular dysfunction and to diagnose and treat the underlying cause with a view to increasing survival.¹⁹⁻²²The management of cardiac arrest survivors without STE, however, is controversial, with a less time-sensitive approach to cardiac catheterisation. Because of the lack of randomised data, there has been variable uptake of such a strategy amongst the interventional cardiology community. ILCOR states that randomised trials are therefore essential in this population to determine if timely delivery to a CAC improves survival.²³However, the coordination of this is complex and close interaction is necessary between centres and ambulance services and internally between the emergency department, cardiologists and the critical care team. We performed A(pilot) Randomised tRial of Expedited transfer to a cardiac arrest centre for non-ST elevation OHCA (ARREST) of presumed cardiac cause to assess the safety and feasibility of conducting a large-scale randomised controlled trial in patients without STE.

Methods

This was a pilot multi-centre prospective randomised controlled trial undertaken in London, United Kingdom by London Ambulance Service (LAS) and St Thomas Hospital (for system characteristics see online supplemental information). All adult witnessed out-of-hospital pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF) cardiac arrests without obvious non-cardiac cause (trauma, drowning, suicide, poisoning) attended by the advanced paramedic practitioners in a pre-hospital setting were considered eligible for inclusion. Randomisation was performed following 3 cycles of CPR regardless of return of spontaneous circulation (ROSC). Refractory VF was defined as refractory to shock and drug treatment following 3 cycles of CPR. Patients were excluded from the trial if at the point of randomisation they had evidence of STE on the post-resuscitation ECG, the initial rhythm was asystole or pulseless electrical activity (PEA), a do not attempt resuscitation order was in place or suspected pregnancy.

Before randomisation, patient management followed standard pre-hospital ALS guidelines. Eligible patients were randomly allocated with the use of sequentially numbered opaque, tamper-proof sealed envelopes (sealedenvelope.com) with pre-assigned random permuted blocks of ten, stratified according to site (advanced paramedic car). Randomisation was performed 1:1 to one of two parallel trial arms: intervention or control. The intervention arm consisted of activation of the pre-hospital triaging system (currently routinely in place for STE patients only) with pre-alert and delivery of the OHCA patient to the catheter laboratory at the dedicated CAC (24 hours a day, 7 days a week). Patients were transported to hospital with or without ROSC. Patients who achieved ROSC received guideline-recommended post-resuscitation care including targeted temperature management (36°C 28 hours, followed by gradual rewarming at 0.5°C per hour)²⁴ and goal-directed therapies. These included evaluation and identification of the underlying cause of arrest with access to immediate reperfusion if necessary and maintenance of normocapnia and normoxia with protective ventilation, optimisation of haemodynamics as well as maintenance of normoglycaemia.²⁵

The control arm comprised the current standard of pre-hospital care for patients with cardiac arrest of suspected cardiac aetiology as per LAS Cardiac Care Guidance Protocol (supplemental data). Patients were conveyed to the closest emergency department and management thereafter followed standard hospital protocol. In the absence of non-cardiac cause, and in the absence of futility, coronary angiography was recommended within 48-72 hours in the control arm if not performed sooner (evidence of STE or high-suspicion of on-going infarction at the discretion of the physician).

The primary objective of this pilot trial was to assess the feasibility of a randomised trial in OHCA without STE comparing expedited transfer to a CAC with the current standard of care to assess a difference in 30-day mortality. Feasibility outcome measures included recruitment rate, protocol adherence and the ability to obtain case-report form specific data on participants. The primary clinical endpoint was 30-day all-cause mortality. Secondary clinical endpoints comprised 1) good neurological function at discharge, capped at 30 days according to the cerebral performance category(CPC), the most commonly used post-resuscitation outcome measurement for this purpose.²⁶ 2) The composite of in-hospital major adverse cardiovascular events(MACE) capped at 30 days, defined as: re-infarction²⁷, further revascularisation and bleeding.

Prior to data analysis, the following additions were made to the trial secondary outcomes to capture all adverse events: 1) MACE was modified to include cerebrovascular events – termed MACCE. 2) Sepsis, defined as two or more components of the systemic inflammatory response syndrome.²⁸

Trained research staff at St Thomas Hospital collected trial related data. The trial was managed and coordinated by the London School of Hygiene and Tropical Medicine Clinical Trials Unit (LSHTM CTU). The study was granted ethical approval by the United Kingdom National Research Ethics Committee (REC 13/LO/1508). Due to the specific nature of the trial and the immediacy of the intervention, the committee waived the need for prior informed consent. At the earliest appropriate time, the participant or their legal surrogate were asked for delayed consent. The trial was prospectively registered with the International Standard Randomised Controlled Trials Registry (ISRCTN 96585404).

Statistical Analysis

Statistical analysis, based on intention to treat, was performed using StatPlus (AnalystSoft, USA) and Prism version 7.0 (GraphPad Software Inc, USA). The sample size (n=40) was selected to allow an assessment of the feasibility of recruitment and implementation of trial processes.²⁹ The pilot study was not powered to detect important differences. However, categorical data were compared using Fisher's exact test; continuous data were compared by 2-sample t-test. The treatment groups were compared for the primary endpoint of all-cause mortality 30-days after randomisation using odds ratios with 95% confidence intervals (CI). The Kaplan-Meier survival curves were drawn to assess differences between groups for the time to an event data examining all-cause mortality at 30 days. All p values were 2 sided.

Results

Patient Population and Feasibility

118 cases were screened, of which 63 patients (53%) met eligibility criteria. Forty of the 63 patients (63%) were randomised over two separate time periods: November 2014 to March 2015 (10 patients) and August 2015 to February 2016 (30 patients). Full data were available on 36 patients (90%); reasons for exclusion are detailed in the patient flow diagram (Figure 1), displayed according to Consolidated Standards of Reporting Trials (CONSORT) recommendation. The trial was stopped at 40 patients because the planned sample size to assess trial feasibility was reached. All randomised patients completed the trial. All patients in the Intervention arm were delivered direct to St Thomas Hospital cardiac catheter lab; patients in the control arm were delivered to the emergency department (ED) in one of 6 hospitals in London: St. Thomas Hospital, St. Mary's Hospital, Chelsea and Westminster Hospital, King's College Hospital, Royal Free Hospital, Royal London Hospital. One patient in the control arm did not reach hospital (online supplement). After randomisation, 4 patients (10%) were found to meet exclusion criteria (the presence of ST-elevation on the post-resuscitation ECG). However, for the intention to treat analysis, all patients were analysed in the group they were randomised to regardless of this or eventual crossover or other protocol deviation. Only one patient was identified as having a non-cardiac cause of arrest (end-stage renal failure) and did not survive to hospital. All other patients had a cardiac cause of arrest. One patient had aortic dissection that was managed within the specialist centre, ten patients were identified as having a scar-related arrhythmia either due to previous infarct or heart muscle disease (requiring implantable cardioverter defibrillator implantation on admission) and the rest were directly due to coronary artery disease.

Baseline characteristics, the intervals from cardiac arrest to defined events and ambulance service interventions are shown in Table 1. There were no significant differences between the two treatment groups in terms of baseline characteristics and cardiac arrest background variables. All patients presented with witnessed VF out-of-hospital cardiac arrest. Three patients in each group had ventricular fibrillation that was refractory to shock and drug treatment and were transported to hospital without ROSC.

Angiographic characteristics

The coronary angiographic findings are summarised in Table 2. Time to coronary angiography was shorter in the intervention arm compared with the control arm (100[75 to 113] versus 132[93 to 187]; median difference 32, 95% CI -9 to 101; $P=0.08$). The incidence of culprit artery occlusion (responsible for the OHCA) was 44% in the intervention group versus 50% in the control group (OR 0.6, 95% CI 0.1 to 2.3; $P=0.7$).

Primary and Secondary Clinical Outcomes

The primary clinical endpoint of 30-day all-cause mortality (Table 3) was similar between both study arms (Intervention 9/18, 50% vs. Control 6/15, 44%; OR 0.6, 95% CI 0.2 to 2.9; $P=0.73$). Good neurological function evaluated at discharge, capped at 30 days, was similar in both groups (Intervention 9/18, 50% vs. Control 7/15, 47%; OR 1.1, 95% CI 0.3 to 4; $P>0.99$) (online supplement). The secondary (clinical) composite endpoint of in-

hospital MACCE occurred in 11/18 in the Intervention arm compared with 6/15 in the control arm (61% vs. 53% respectively; OR 1.4, 95% CI 0.4 to 4.9; $P=0.73$). One stroke occurred in the control arm, one patient in the intervention arm and two in the control arm underwent further revascularisation and minor bleeding occurred in one patient in the intervention arm. The secondary endpoint of 6-month all-cause mortality was 9/17 (53%) in the intervention arm and 6/10 (60%) in the control arm (OR 0.75, 95% CI 0.2 to 3.8; $P>0.99$). One third of patients in both groups developed sepsis. Vascular complications occurred in one patient in the control arm. Four patients in the intervention group and two patients in the control group required mechanical circulatory support in the form of intra-aortic balloon pump insertion. Length of stay was the same in the two groups (intervention: 4.5, versus control: 4.5, median difference 0, 95% CI -2 to 8; $P=0.19$).

The Kaplan-Meier 30-day survival curve is shown in Figure 2 (intervention versus control: HR 1.7, 95% CI 0.3 to 10.5; $P=0.6$). In both study arms, a marked attrition in survival was seen between Day 0 and Day 4, with 25% of patients dead in the Intervention arm and 17% in the Control arm (overall 21%). No further patients died between Day 4 and Day 30. Administration of amiodarone was associated with increased 30-day mortality (HR 11.5, 95% CI 1.04 to 126; $P=0.04$). Pre-hospital ROSC (HR 0.1, 95% CI 0.01 to 0.7; $P=0.02$), and cardiac arrest in a public location (HR 0.05, 95% CI 0.004 to 0.45; $P=0.01$) were associated with a lower mortality. The performance of coronary angiography was found to negatively influence 30-day mortality (HR 0.15, 95% CI 0.03 to 0.71; $P=0.02$); however, after adjustment for pre-hospital factors, there was no influence on 30-day mortality (HR 0.41, 95% CI 0.05 to 3.5; $P=0.4$), Figure 3.

Discussion

We demonstrated that it is possible to complete a randomised controlled trial comparing a pre-hospital triage system involving delivery of the OHCA patient to a CAC with access to 24/7 interventional cardiology facilities and receipt of a post-cardiac arrest care bundle with the current standard of care in a population of OHCA patients without STE. The main finding of this pilot trial is that performing a large-scale randomised controlled trial is safe, feasible and acceptable. The feasibility of randomisation was demonstrated as follows: (1) recruitment of all adult witnessed shockable OHCA of presumed cardiac cause exceeded the expected rate. (2) It was possible to set up a fast track, rapid intervention service in a single CAC 24/7. (3) Protocol adherence was excellent in the intervention arm. (4) Data completeness was acceptable with documentation of the primary outcome in 83% and secondary outcomes in 80%.

Based on the findings of the trial pilot, the decision to exclude the refractory cohort from the main trial was made based on 1) logistical challenges of on-scene extrication, transport and performing coronary angiography during mechanical CPR (m-CPR). 2) Poor outcomes relative to the cohort of patients achieving ROSC. 3) The identification that this was a predictor of 30-day mortality. Furthermore, not all frontline vehicles carry m-CPR devices, which may prevent shock-refractory patients receiving the same treatment in the main trial. The PARAMEDIC trial (LUCAS m-CPR device) showed a 5% lower survival rate (significant) in patients with shockable rhythms who received mechanical CPR, although this was not the primary objective of the trial, and

should be interpreted with caution.³⁰ Furthermore, removal of this cohort will reduce the likelihood of post randomisation identification of STE (10%).

Outcome was ascertained in 83%; to improve this we will make use of the NHS information centre; in the PARAMEDIC trial, this enabled 99% follow-up at 30-days.³⁰ Where data cannot be collected in hospital we plan to make use of the London Ambulance Clinical Audit and Research Unit (CARU) and National Institute for Cardiovascular Outcomes Research (NICOR). Because of the geographical position of St Thomas Hospital, a large proportion of the standard of care arm were delivered to a CAC; we anticipate that expanding the trial across London will reduce the proportion of patients in the control arm taken straight to the cardiac catheterisation laboratory.

The International Liaison Committee on Resuscitation (ILCOR) suggests transport of all post-arrest patients to a cardiac arrest centre with 24/7 access to interventional cardiology facilities.¹⁹⁻²² There has been variable uptake of such a strategy in this cohort; this may be due in part to the lack of randomised data, the need for coordination of organised systems of care, and the heterogeneity of the non-STE population; thus emphasising the need for a randomised controlled trial.

Our study is consistent with well-established predictors of survival, including ROSC pre-hospital and cardiac arrest in a public location. The predictor of mortality identified was administration of amiodarone, this is likely to represent refractory arrhythmia rather than the effect of amiodarone itself. These are supported by findings in the recently published "amiodarone versus lignocaine and placebo trial in OHCA", where no difference in survival was shown, with a higher mortality in those with unwitnessed arrest.³¹ Coronary angiography was performed in all patients in the intervention group and just under 80% of control, suggesting that coronary angiography was clinically indicated in the latter. The time to coronary angiography was shorter in the intervention arm because of immediate delivery to a CAC, but this did not reach statistical significance in these few patients. In those who underwent coronary angiography, significant coronary disease was identified in two thirds of patients, with a culprit lesion in just over half, which is consistent with published registry data.^{16,32} However should be interpreted with caution because this was a small patient cohort that may not be representative of the patient population. The findings from this pilot also suggest that the absence of STE on the post-arrest ECG does not exclude acute ischemia.¹⁵ The overall mortality, albeit low, is representative of the VF OHCA population that achieves ROSC pre-hospital and is consistent with previous figures published by the London Ambulance Service.³³

Limitations

This study was a pilot randomised trial to demonstrate safety and feasibility; the study was not powered to show a difference in 30-day mortality, neurological endpoints or the composite of in-hospital MACCE. The full planned trial with a sample size of 860, will aim to address these questions. The catchment area around St Thomas Hospital was small and may not be representative of the population. Although this pilot provided an indication of

the underlying event rate and incidence of occlusive coronary artery disease, the effect size and therefore sample size calculations were based on a combination of studies. These included the above pilot findings, Pan-London Annual OHCA audit data, published registry data (incidence of occlusive disease in OHCA in absence of STE) and randomised trials of reperfusion therapy.^{13,33-35} Based on findings from the trial pilot, inclusion criteria were amended to remove the shock-refractory cohort from the main trial because logistical challenges of managing these patients, and in order to reduce the likelihood of post-randomisation identification of STE. Delayed prognostication (≥ 72 hours) to prevent the premature withdrawal of life-sustaining treatment was not formally instituted in the pilot as this was not the current standard of care; however this will be mandated during the full trial.³⁶

Conclusions

This pilot study demonstrated that a large-scale randomised trial comparing the delivery of a cardiac arrest patient without STE to the catheter laboratory at a dedicated cardiac arrest receiving centre with a view to immediate reperfusion and delivery of post-resuscitation care, compared with standard care, is safe and feasible.

Conflicts of interest: none

Disclosure: The authors have no disclosures or conflicts of interest to share.

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References

1. Berdowski J, Berg RA, Tijssen JGP, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation* 2010;81(11):1479–87.
2. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 2014;129(3):399–410.
3. Perkins GD, Brace-McDonnell SJ, OHCAO Project Group. The UK Out of Hospital Cardiac Arrest Outcome (OHCAO) project. *BMJ Open* 2015;5(10):e008736.
4. Sasson C, Rogers MAMM, Dahl J, Kellermann AL. Predictors of Survival From Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes* 2009;3(1):63–81.
5. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA : the journal of the American Medical Association* 2010;304(13):1447–54.
6. Lick CJ, Aufderheide TP, Niskanen RA, et al. Take Heart America: A comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. *Critical care medicine* 2011;39(1):26–33.

7. Lurie KG, Idris A, Holcomb JB. Level 1 cardiac arrest centers: learning from the trauma surgeons. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2005;12(1):79–80.
8. Nolan JP, Lyon RM, Sasson C, et al. Advances in the hospital management of patients following an out of hospital cardiac arrest. *Heart (British Cardiac Society)* 2012;98(16):1201–6.
9. Kern KB. Cardiac receiving centers: beyond hypothermia. *Current opinion in critical care* 2012;18(3):246–50.
10. Jacobs AK. Regional systems of care for patients with ST-elevation myocardial infarction: being at the right place at the right time. *Circulation* 2007;116(7):689–92.
11. Acker JE, Pancioli AM, Crocco TJ, et al. Implementation strategies for emergency medical services within stroke systems of care: a policy statement from the American Heart Association/American Stroke Association Expert Panel on Emergency Medical Services Systems and the Stroke Council. *Stroke*. 2007;38(11):3097–115.
12. Cameron PA, Gabbe BJ, Cooper DJ, Walker T, Judson R, McNeil J. A statewide system of trauma care in Victoria: effect on patient survival. *Med J Aust* 2008;189(10):546–50.
13. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;73(1):29–39.
14. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *The New England journal of medicine* 2006;355(1):41–50.
15. Spaulding CM, Joly LM, Monchi M, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *The New England journal of medicine* 1997;336(23):1629–33.
16. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac Arrest) registry. *Circulation: Cardiovascular Interventions* 2010;3(3):200–7.
17. Kern KB, Rahman O. Emergent percutaneous coronary intervention for resuscitated victims of out-of-hospital cardiac arrest. *Catheter Cardiovasc Interv* 2010;75(4):616–24.
18. Reynolds JC, Callaway CW, El Khoudary SR, Moore CG, Alvarez RJ, Rittenberger JC. Coronary angiography predicts improved outcome following cardiac arrest: propensity-adjusted analysis. *Journal of intensive care medicine* 2009;24(3):179–86.
19. Peberdy MA, Donnino MW, Callaway CW, et al. Impact of Percutaneous Coronary Intervention Performance Reporting on Cardiac Resuscitation Centers: A Scientific Statement From the American Heart Association. *Circulation* 2013;
20. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010;122(18 Suppl 3):S768–86.
21. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation. *Circulation* 2008;118(23):2452–83.
22. Noc M, Fajadet J, Lassen JF, et al. Invasive coronary treatment strategies for out-of-hospital cardiac

- arrest: a consensus statement from the European association for percutaneous cardiovascular interventions (EAPCI)/stent for life (SFL) groups. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2014;10(1):31–7.
23. Nikolaou NI, Welsford M, Beygui F, et al. Part 5: Acute coronary syndromes: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation* 2015;95:e121–46.
 24. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. *The New England journal of medicine* 2013;:131117131833001.
 25. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive care medicine*. 2015;41(12):2039–56.
 26. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *American Heart Association, Inc*; 2015. p. 1286–300.
 27. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *European heart journal* 2012;33(20):2551–67.
 28. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *American Medical Association*; 2016. p. 801–10.
 29. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *Journal of Clinical Epidemiology* 2012;65(3):301–8.
 30. Perkins GD, Lall R, Quinn T, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *Lancet* 2015;385(9972):947–55.
 31. Kudenchuk PJ, Daya M, Dorian P, Resuscitation Outcomes Consortium Investigators. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. *The New England journal of medicine* 2016;375(8):802–3.
 32. Kern KB, Lotun K, Patel N, et al. Outcomes of Comatose Cardiac Arrest Survivors With and Without ST-Segment Elevation Myocardial Infarction: Importance of Coronary Angiography. *JACC Cardiovasc Interv* 2015;8(8):1031–40.
 33. Fothergill RT, Watson LR, Chamberlain D, Viridi GK, Moore FP, Whitbread M. Increases in survival from out-of-hospital cardiac arrest: a five year study. *Resuscitation* 2013;84(8):1089–92.
 34. Patterson T, Whitbread M, Clayton T. TCT-268 Immediate coronary angiography after ventricular fibrillation out-of-hospital cardiac arrest (ARREST): A Randomised Controlled Trial (ISRCTN 96585404). *Journal of the ...* 2015;
 35. Franzosi MG, Santoro E, De Vita C, et al. Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della

Sopravvivenza nell'Infarto-1 study. The GISSI Investigators. *Circulation* 1998;98(24):2659–65.

36. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Intensive care medicine* 2014;40(12):1816–31.

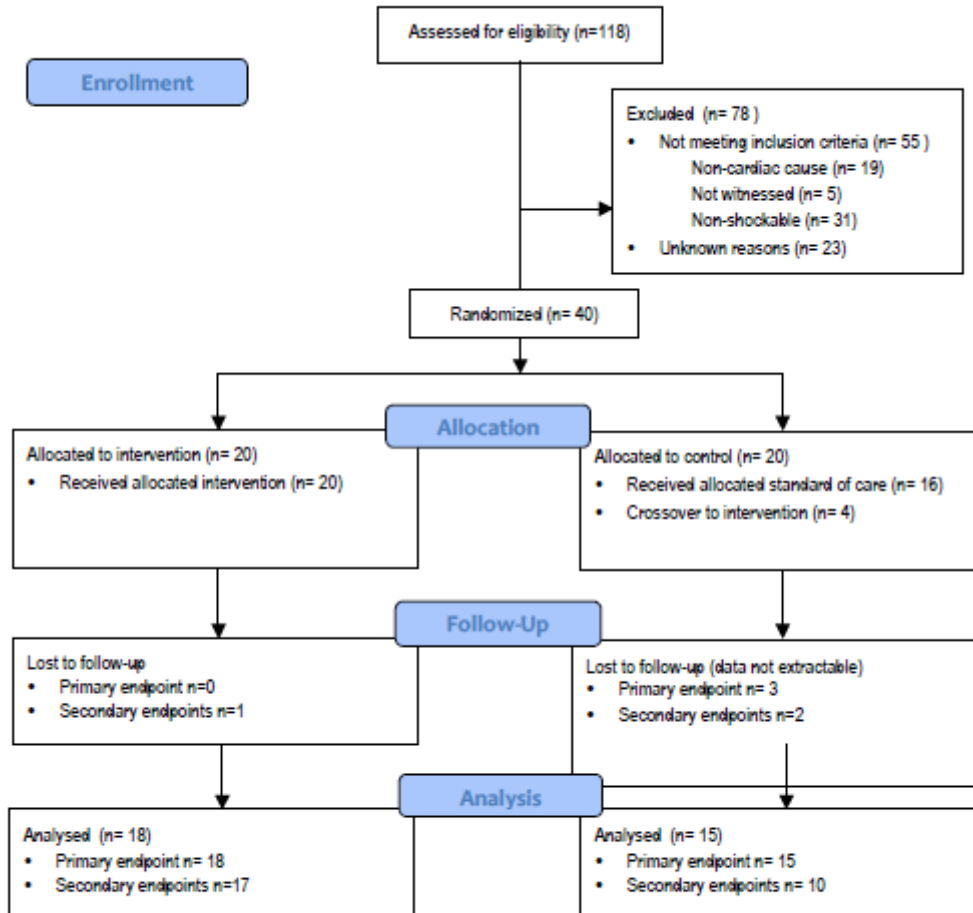


Figure 1 Participant flow diagram: as per CONSORT guidelines.

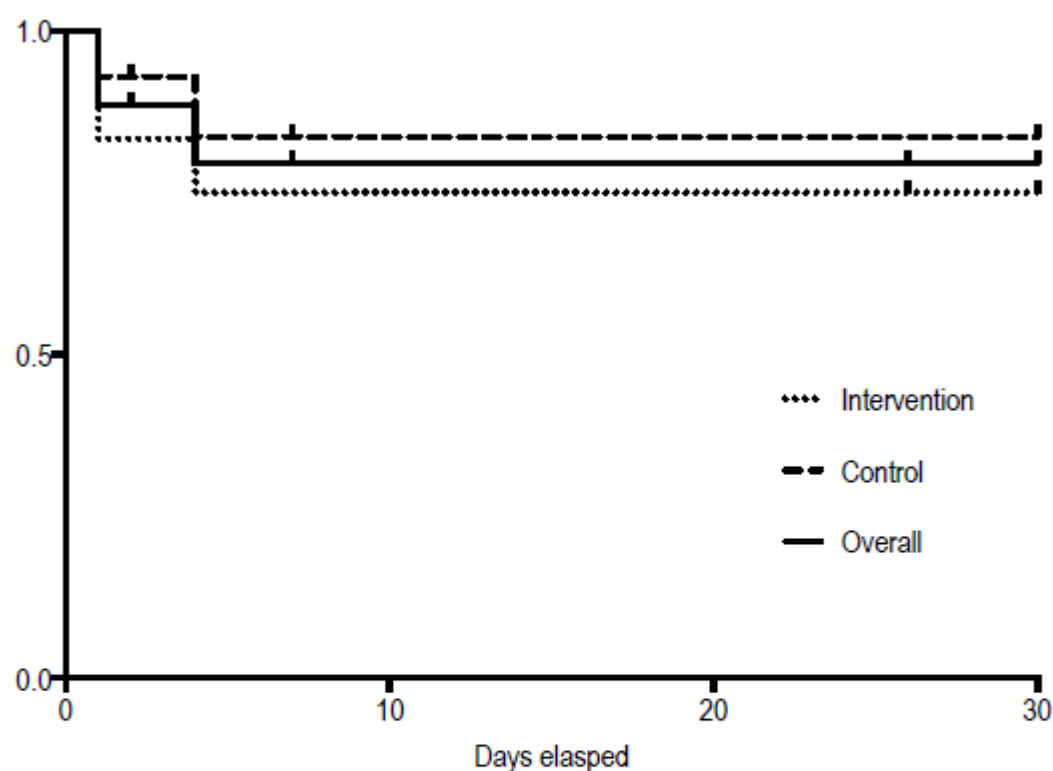


Figure 2 Survival curves for the whole cohort of 40 patients. Event rate was calculated by Kaplan-Meier method; survivor function (solid line) and survival rates according to randomization arm: Intervention (dotted line), Control (broken line) Event rates were calculated by the Kaplan-Meier method, HR 1.7 (95% CI 0.3 to 10.5) and compared with the use of the Log-rank test $P = 0.6$.

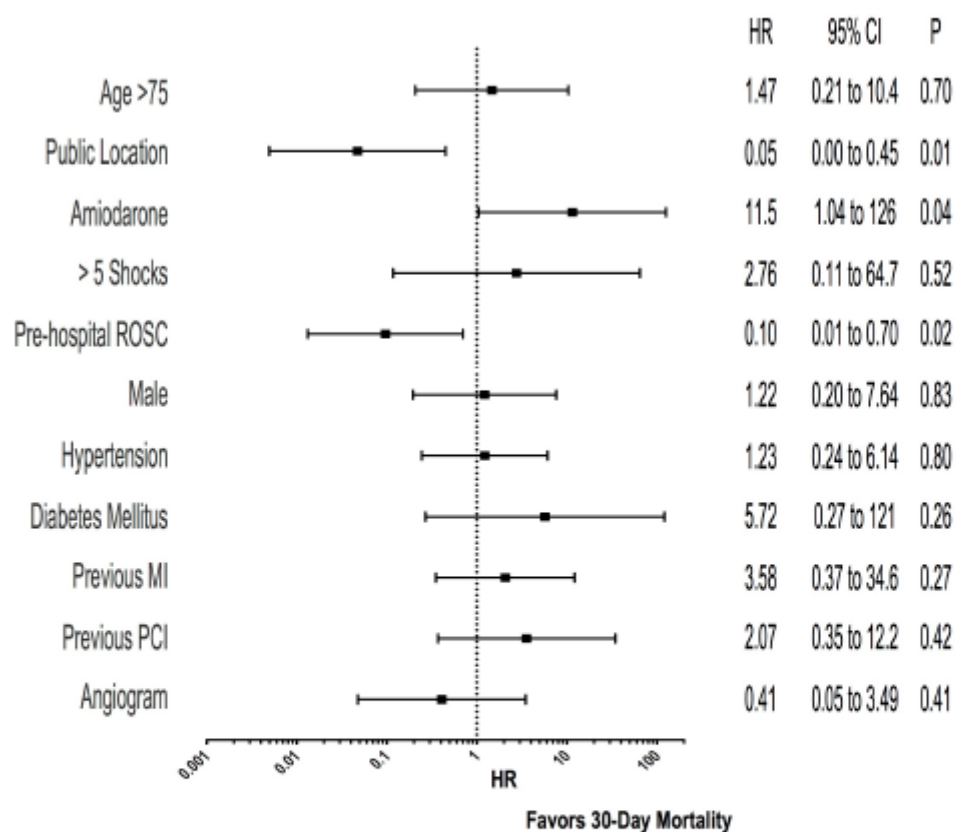


Figure 3. Cox proportional hazards model, presented as a forest plot, for predictors for 30-mortality; abbreviations: ROSC return of spontaneous circulation, MI myocardial infarction, PCI percutaneous coronary intervention.

	Total	Intervention	Control	P value
Angiogram	32/36 (89%)	18/18 (100%)	14/18 (78%)	0.10
Time to Angiography (minutes)		100; 75 to 113	132; 93 to 187	0.08
Coronary Artery Disease (>50% stenosis)	20/32 (63%)	12/18 (67%)	8/14 (57%)	0.72
Number of diseased vessels				
0	10/32 (31%)	6/18 (33%)	4/14 (21%)	>0.99
1	4/32 (13%)	2/18(11%)	2/14 (14%)	>0.99
2	4/32 (13%)	2/18(11%)	2/14 (14%)	0.47
≥3	12/32 (38%)	8/18 (44%)	4/14 (29%)	0.47
Unknown	2/32 (6%)	0/32 (0%)	2/14 (6%)	0.18
Culprit: Revascularisation	15/32 (47%)	8/18 (44%)	7/14 (50%)	0.71
1. PCI	13/15 (87%)	7/8 (88%)	6/7 (86%)	>0.99
LMS	0/13 (0%)	0/7 (0%)	0/6 (0%)	>0.99
LAD	5/13 (38%)	3/7 (43%)	2/6 (33%)	>0.99
Cx	3/13 (23%)	1/7 (14%)	2/6 (33%)	0.56
RCA	5/13 (38%)	3/7 (43%)	2/6 (33%)	>0.99
2. CABG	2/15 (13%)	1/8 (13%)	1/7 (14%)	>0.99

Table 1Angiographic characteristics of the intervention and control arm. Categorical variables are presented as counts and percentages n/N (%); times are displayed as mean±SD. Abbreviations: PCI percutaneous coronary intervention, LMA left main stem, LAD left anterior descending artery, CX circumflex artery, RCA right coronary artery, CABG coronary artery bypass grafting.

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	Total	Intervention	Control	OR (95% CI)*	Pvalue
Primary Endpoint					
30-day all cause mortality	15/33 (45%)	9/18 (50%)	6/15 (40%)	0.6 (0.2 to 2.9)	0.73
Secondary Endpoints					
CPC 1/2 at 30 days	16/32 (50%)	9/18 (50%)	7/14 (50%)	1.0 (0.3 to 3.6)	>0.99
MACCE*	19/33 (58%)	11/18 (61%)	8/15 (53%)	1.4 (0.4 to 4.9)	0.73
Death	15/33 (45%)	9/18 (50%)	6/15 (40%)	0.6 (0.2 to 2.9)	0.73
MI	0/33 (0%)	0/18 (0%)	0/15 (0%)	N/A	>0.99
Further revascularization	3/33 (9%)	1/18 (6%)	2/15 (13%)	0.4 (0 to 3.7)	0.58
Stroke	1/33 (3%)	1/18 (6%)	0/15 (0%)	N/A	>0.99
Bleeding	1/33 (3%)	1/18 (6%)	0/15 (0%)	N/A	>0.99
Vascular complications	1/33 (3%)	0/18 (0%)	1/15 (7%)	0 (0 to 7.5)	0.5
6-month all cause mortality	15/27 (56%)	9/17 (53%)	6/10 (60%)	0.75 (0.2 to 3.8)	>0.99
Length of Stay*	4.5 (0 to 11)	4.5 (0 to 7.3)	4.5 (0 to 19)	0 (-2 to 8)	0.19
CPR Related Complications	1/33 (3%)	1/18 (6%)	0/15 (0%)	N/A	>0.99
Renal Replacement Therapy	2/33 (3%)	1/18 (6%)	1/15 (7%)	0.8 (0 to 17)	>0.99
Sepsis	11/33 (33%)	6/18 (33%)	5/15 (33%)	1.0 (0.2 to 4.5)	>0.99
Mechanical Circulatory Support	6/33 (18%)	4/18 (22%)	2/15 (13%)	1.6 (0.3 to 9.5)	0.68

Table 3 Primary and secondary outcomes, length of stay and other in-hospital complications described overall and for both arms of the trial. Categorical variables are presented as counts and percentages n/N (%); *days are displayed as median and interquartile range (IQR). Abbreviations: CPC cerebral performance category score, MACCE major adverse cardiovascular and cerebrovascular events, CPR cardiopulmonary resuscitation.